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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/012,369	01/23/98	MARGOLIS	B 231/198

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EXAMINER	
HUNT, J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/012,369	Marglis et al.
Examiner	**Art Unit**
Jennifer Hunt	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *3-16-01 and 7-16-01* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26-35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26-35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Acknowledgment is made of applicant's cancellation of claims 1-12 and 19-25, and addition of new claims 26-35. Claims 26-35 are pending in the application and addressed herein.

Claim Rejections - 35 U.S.C. § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 26-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. The term "therapeutically effective amount" in claims 26-35 is a relative term which renders the claim indefinite. The term "therapeutically effective amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, it is not clear what therapeutic effect is being sought, and thus it cannot be determined at what point the therapy would be considered "effective".

4. Claims 26-35 are unclear in the recitation of the term "agent". The metes and bounds of an "agent" cannot be determined. It is not clear what would be considered an agent and what would not.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 26-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to a method of altering signal transduction in an APB domain containing signal transduction pathway comprising administering to a patient a therapeutically effective amount of an agent which decreases binding between an APB recognition region in a first protein and an APB domain present in a second protein.

APB domain is broadly defined as having at least 20% sequence identity to the APB domain present in Shc (ie: AA's 46-209 of $p52^{shc}$) and "can" play a role in signal transduction. Thus the term "APB domain" encompasses a large number of proteins.

Further, the method is drawn to "altering" signal transduction, and thus encompasses both enhancing and decreasing signal transduction, as well as any other sort of "alteration".

Additionally, an "agent" is not defined in the specification and thus the scope of such cannot be determined.

Thus the claims are drawn to a method of determining how an "agent" which is not clearly defined "alters' (either increasing or decreasing or any other affect) signal transduction by binding to an "APB domain" (when APB domain encompasses an innumerable quantity of proteins).

The specification teaches that two specific regions of Shc (Shc 1-209 and Shc 46-209) (which would be considered APB domains) bind to phosphorylated EGFR, HER2/neu, and TrkA (which would be considered to contain APB recognition regions). The specification fails to teach any other "APB domains", nor does it provide guidance as to any other domains which would be expected to function as the exemplified embodiments do.

Prediction of how variations in protein sequence will affect function is complex and outside of the realm of routine experimentation as set forth below:

Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain

functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases

is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3).

Further, no other "APB recognition regions" are taught or suggested, absent the exemplified EGFR, HER2/neu, and TrkA. No "agent" is administered, and thus it is not clear how any agent would affect binding between an APB domain and an APB recognition region, nor is it clear if binding was affected, if the affect would be capable of altering signal transduction.

As set forth in previous Office Actions, there is insufficient evidence provided to support a role for APB binding in the mediation of signal transduction, because there is no objective evidence that disruption of APB binding to EGFR, HER2/neu, TrkA, or any other protein which contains an "APB recognition region" results in the predictable alteration of signal transduction. No therapeutic agents which promote or disrupt such binding are provided. Further, it is not disclosed what region of the EGRF, HER2/neu and TrkA receptors are bound. Neither is the role of binding in signal transduction suggested or provided. In fact, the specification teaches that it is art-known that specific binding is determined by SH2 domains, but that the physiological role of APB binding is unknown (see page 57 and page 64 of the specification). Further, the specification warns that the data presented must be approached with caution and that the

interactions seen instantly, involving protein fragments may not be representative of the full length situation (see page 63 of the specification).

Further, the claims encompass the experimental and unpredictable field of in vivo therapy for mammals. An article by *Dermer (BIO/TECHNOLOGY, Vol 12, page 320, 03/1994*) is cited in order to establish the general state of the art and the level of predictability of in vivo therapy. Dermer teaches that "What is significant in culture, for example immunotherapy's killing power or the transformation of 3T3 cells by a mutated proto-oncogene, simply does not have the same significance for cells in vivo."

Those of skill in the art recognize that in vitro assays are generally useful to screen the effects of agents on target cells. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo experiment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to mammal or human therapeutic with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state.

Further a therapeutic agent must accomplish several tasks to be effective: it must be delivered into circulation and interact at the proper site of action, and it must do so at a therapeutic concentration and remain effective for a sufficient period of time. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In assays, the agent is in contact with the cells during the entire exposure period, whereas in the case of in vivo therapy, exposure at the target site may be delayed or insufficient. Discussing agents used to treat cancer, *Jain,*

Science Vol 271, 23 February 1996, pages 1079-1080 states that "Because of their potent effect on cancer cells in vitro and in some in vivo tumor systems, these agents have been heralded as breakthrough drugs, or "magic bullets" and have been enthusiastically accepted as such by policy makers, investors, and the general public. Although the potential for using these agents in cancer therapy is great and almost certainly justified, clinical results to date have not met the high expectations extrapolated from carefully planned and performed preclinical studies." *Jain , R. K. (Cancer and Metastasis Reviews, 9:753-266, 1990)* teaches that the efficacy in cancer treatment of novel therapeutic agents such as monoclonal antibodies, cytokines and effectors cells has been limited by their inability to reach their target *in vivo* in adequate quantities. Three physiological factors responsible for the poor localization of macromolecules in tumors have been identified: (I) heterogeneous blood supply, (ii) elevated interstitial pressure which lowers fluid extravasation, and (iii) large transport distances in the interstitium. Furthermore, the average vascular surface area decreases with tumor growth, hence reducing transvascular exchange in large tumors compared to smaller tumors. The molecule may also bind non-specifically to proteins or other tissue components; bind specifically to the target and or be metabolized, which further lowers the effective diffusion rate by reducing the amount of mobile molecule. Finally, although the effector cells are capable of active migration, peculiarities of the tumor vasculature and interstitium may be also responsible for poor delivery.

Therefore one of skill in the art would conclude that in vivo therapy of signal transduction disorders including cancer is an unpredictable and complex art and that in vitro tests are not sufficient to enable in vivo treatments.

Further, the specification does not disclose treatment of any cells, but rather the speculative possibility that there might be a treatment which could affect binding activity which was only tested in vitro.

Therefor for reasons set forth above, and in previous Office Actions, one of skill in the art would not be enabled to practice the invention as claimed.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

September 24, 2001

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